Derivation and characterization of human ES cells from FSHD embryos

Grant Award Details

Derivation and characterization of human ES cells from FSHD embryos

Grant Type: SEED Grant

Grant Number: RS1-00455

Investigator:

Name:	Kyoko Yokomori
Institution:	University of California, Irvine
Type:	PI

Disease Focus: Genetic Disorder, Muscular Dystrophy, Skeletal/Smooth Muscle disorders

Human Stem Cell Use: Embryonic Stem Cell

Cell Line Generation: Embryonic Stem Cell

Award Value: $607,200

Status: Closed

Progress Reports

Reporting Period: Year 2

View Report

Grant Application Details

Application Title: Derivation and characterization of human ES cells from FSHD embryos

Public Abstract: Facioscapulohumeral muscular dystrophy (FSHD) is the third most common hereditary muscular dystrophy. It is autosomal dominant, meaning that if one of the parents has the disease, their children have a 50:50 chance of getting it, too. FSHD is characterized by progressive weakness and atrophy of facial, shoulder and upper arm musculature, which can spread to other parts of the body. In some cases, it is accompanied by hearing loss and, in severe cases, mental retardation. There is no cure or treatment of this disease since the gene(s) responsible for this disease has not been identified. One thing that is clear is that the majority of FSHD is linked to a decrease in the number of repeats of a DNA sequence called D4Z4 located at the end of chromosome 4. When shortening of this repeat region occurs in either chromosome 4, the person gets FSHD. However, it is unclear how shortening of this repeat leads to the disease. We found that this D4Z4 repeat cluster contains “heterochromatin” structure, which is associated with gene silencing. This heterochromatin structure includes specific methylation of histone H3 and the recruitment of heterochromatin binding proteins HP1 and cohesin. HP1 is known to be required for gene silencing. Importantly, we found that this heterochromatin structure is uniquely lost in FSHD patient cells. Surprisingly, the minor population of FSHD patients who do not exhibit any repeat shortening also lack this heterochromatin structure in the D4Z4 repeat on chromosome 4. Therefore, FSHD is a “heterochromatin abnormality” disease, in which loss of heterochromatin at D4Z4 repeats leads to disease manifestation. We hypothesize that the normal heterochromatin structure spreads silencing effects on to other genes, but in FSHD this effect is lost and these genes that are normally silent may be abnormally expressed. Since we found that this heterochromatin structure is already established in embryonic stem (ES) cells under normal circumstances, it is of vital importance to examine this process in FSHD ES cells. This would be important to understand how heterochromatin establishment is compromised during development and, as a result, which genes are affected. However, no FSHD ES cells are currently available. Generous and courageous families with FSHD in their history donated in vitro fertilized embryos for research use in the hope of improving the life of FSHD patients in the future. Therefore, our major goal is to establish FSHD ES cell lines not only for our research, but also for use in the FSHD research community. We hope to optimize a protocol to differentiate these cells into skeletal muscle cells for a comparative analysis between normal and FSHD ES cells during development. I believe that the proposed project will make significant contributions to understanding the etiology and pathogenesis of FSHD as well as to possibly develop therapeutic strategies to improve the physical functioning of FSHD patients.

Statement of Benefit to California:	Facioscapulohumeral dystrophy (FSHD) is the third most common hereditary muscular dystrophy in the United States. California is the most represented state in the U.S. in terms of membership in the FSH Society. Almost 250 families in California with an average of 3-4 affected members per family belong to the FSH Society, which would translate to 750 to 1,000 total registered patients. FSHD is reported to have a 1 in 20,000 incidence. However, the Society estimates that the actual incidence is probably considerably higher, with a likely incidence of 1/7,000. This higher estimate is based on clinician expert opinion that FSHD is at least three times more prevalent due to misdiagnosis, which reflects the difficulty associated with recognizing those patients with a mild clinical disease presentation. This is consistent with the opinions of some people who track FSHD cases that improved molecular diagnostic techniques will give a more accurate assessment of the full range of this disease in the population. Since this disease is dominantly inherited, a large family can have a significant number of affected individuals. In one documented case a family of 2,500 people traced to a settler who had FSHD had1600-1700 affected members, many of whom ultimately moved to California. Many families affected by this disease are reluctant to come forward to seek help, and therefore are not included in the membership rolls of the FSH Society. FSHD is not necessarily lethal and many patients must live and cope with progressive disability during their lives without any effective treatment. There is no effective treatment because the disease mechanism is unclear. The fact that the upper limbs are predominantly affected suggests that the abnormality may be initiated during embryonic development. Thus, the proposed project to obtain FSHD ES cells is critical for studying this crucial time point in manifestation of the disease. We plan to make these cells available to scientists in the FSHD field to further facilitate investigation of many different aspects of FSHD pathogenesis. We also hope that these cells become valuable reagents for development of better molecular diagnostics as well as fostering new ideas concerning possible treatment strategies. The primary goal is to offer new insight into improving the lives of the many FSHD patients in California and across the international community.